UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,365	11/09/2005	Inga Reynisdottir	2345.2046-007	4456

21005 7590 05/08/2009

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
05/08/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,365	REYNISDOTTIR ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,23,24,27-42 and 44-50* is/are pending in the application.

4a) Of the above claim(s) *2,4-21,23,24,30-42,44,49 and 50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,27-29 and 45-48* is/are rejected.

7)☒ Claim(s) *3 and 45* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/05; 5/15; 2/29; 7/31*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group I, marker DG5S881 in the reply filed on 5/16/08 is acknowledged.

Claim Objections

2. Claims 3 and 45 are objected to because they refer to tables and figures. MPEP 2173(s) states "Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience."

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 27, 28, and 29 rejected under 35 U.S.C. 102(b) as being anticipated by Holloway et al. (WO 01/46418, as cited in IDS).

Holloway et al. methods for using probes and primers to detect ZSLIT3 expression. ZSLIT3 is "a SLIT-3" nucleic acid, as evidenced by it's name. Holloway teach that probes can be derived from the nucleotide sequence taught in their specification, in particular their SEQ ID NO: 1 or 3 (page 69 and 89. Holloway hybridized to tumor tissues and the hybridized complex detected by in situ hybridization, or that ZSLIT3 sequences can be detected by PCR

amplification (page 69). Holloway teaches a PCR technique for diagnostic assays which includes a PCR step, hybridization with a probe (which is a nucleic acid comprising a contiguous nucleotide sequence which is complementary to a part of a SLIT-3 sequence), and detection of they hybridization complex (page 90-91). Thus, the teachings of Holloway et al. anticipate claims 27-29.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 3, 45, 46, 47, and 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims are drawn to methods for diagnosing a susceptibility to Type II diabetes comprising detecting a polymorphism in “a SLIT-3 nucleic acid," wherein the presence of the polymorphism is indicative of Type II diabetes, or to screening for “at risk haplotypes” of type II diabetes. Included in this rejection is a claim that is generic as to the polymorphism or haplotype that is detected (claims 1 and 46-48), as well as claims which recite a variety of different polymorphisms and/or haplotypes in the alternative (Claims 3 and 45). For the latter

claims, a restriction requirement was set forth, and applicant elected for prosecution the subcombination where the polymorphism is DG5S881. The written description of the generic claim as well as of the elected embodiment have been considered in this rejection.

The specification teaches that the term "SLIT-3 nucleic acid" refers to a molecule encoding a SLIT-3 polypeptide, and can include all or a portion of the coding sequence and can further comprise additional non-coding sequences such as introns and non-coding 3' and 5' sequences. The specification provides an exemplary SLIT-3 nucleic acid in figure 1 (namely SEQ ID NO: 1). The specification teaches that SLIT3 is a rather big gene that extends over 600 kb. There is no definition in the specification as to what critical features must be present to identify a polypeptide as a "SLIT-3 polypeptide." There is no description of SLIT-3 nucleic acids from non-human animals that may develop type II diabetes, nor is there description of polymorphisms naturally occurring in these animals.

The recitation step requiring the detection of "a polymorphism" that is "indicative of Type II diabetes" or an "at risk haplotype" is a recitation of a product to be detected that is identified by its function. There is no teaching in the specification as to common features of all possible polymorphisms haplotypes within instant SEQ ID NO: 1 or any other molecule that falls within the recitation of a SLIT-3 nucleic acid that have the function of being indicative of type II diabetes. The specification teaches the testing of 106 different polymorphic markers (29 microsatellites and 77 SNP) and found that only thirteen of these demonstrated a statistically significant relationship with type II diabetes. Further, six of these thirteen are microsatellite markers, and for these, incomplete disclosure as to the This exemplifies that not all polymorphisms within the SLIT-3 gene are associated with Type II diabetes. The specification

gives ten haplotypes that are more frequently present in individuals with Type II diabetes, but there is no apparent common structural feature among these haplotypes. And, these haplotypes are comprised of microsatellite alleles for which there is no adequate written description. There is no art-recognized correlation between particular structures in human or non-human SLIT-3 nucleic acids and type II diabetes, based on which those of ordinary skill in the art could predict which as yet unidentified polymorphisms in human or non-human SLIT-3 are indicative of type II diabetes.

There is no description of additional polymorphic sites or haplotypes that exist in nature that are indicative of type II diabetes, and there is no description of how the structure of SEQ ID NO: 1 relates to the structure of different disease related alleles. The general knowledge in the art concerning polymorphisms or type II diabetes does not provide any indication of how the structure of the disclosed alleles and haplotypes is representative of other unknown alleles or haplotypes having concordant or discordant functions. The common attributes of the genus are not described and the identifying attributes of individual alleles or haplotypes that are indicative of type II diabetes are not identified. The nature of alleles and haplotypes is that they are variant structures where the structure and function of one does not provide guidance to the structure and function of others. In other words, the existence of other alleles and haplotypes of those alleles is unpredictable and the structure of other alleles, if they exist, is also unpredictable. In addition, according to the standard definition, the genus might include members that have widely divergent functional properties. One of skill in the art would conclude that the applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claim.

Regarding the elected subcombination- namely the microsatellite marker DG5S881, the specification recites a sequence identified as DGS881 in Figure 12D (SEQ ID NO: 227). The specification is silent as to the alleles of this marker that are present in human populations, and in particular, the alleles that are indicative or diagnostic of type II diabetes. The specification teaches that all markers with the "DG" identifier were designed at decode genetics. Further, the specification provides results for all SNP that were statistically significant in a single-marker analysis, and DG5S881 is not among the listed markers (see Table 4). Thus, there is not adequate written description of methods for detecting disease associated alleles of this microsatellite marker, because no description of those alleles is given.

7. Claims 1, 3, 45, 46, 47, and 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.
The claims are drawn to methods for the diagnosing a susceptibility to type II diabetes in an individual via the detection of a polymorphism or haplotype of the SLIT-3 gene or nucleic acid that is indicative of susceptibility for disease. The nature of the invention, therefore, requires the knowledge of robust and reliable relationship between alleles or haplotypes in SLIT-3 nucleic acids and susceptibility to type II diabetes.

Included in this rejection is a claim that is generic as to the polymorphism or haplotype that is detected (claims 1 and 46-48), as well as claims which recite a variety of different polymorphisms and/or haplotypes in the alternative (Claims 3 and 45). For the latter claims, a restriction requirement was set forth, and applicant elected for prosecution the subcombination

where the polymorphism is DG5S881. The lack of enablement for the generic claim as well as of the elected embodiment have been considered in this rejection.

The specification teaches analysis of the human genome for regions of the genome associated with susceptibility to type II diabetes, narrowing down the region of linkage to 5Q35, and in particular narrowing the region further to a region which includes SLIT-3. Table 2 provides a list of haplotypes that show strongest association to non-obese diabetes, while Table 4 shows a list of significant single-marker allelic association results with SLIT-3. None of these demonstrate that the elected subcombination, namely, namely the DG5S881 microsatellite is associated with increased or decreased susceptibility to type II diabetes.

The rejected claims encompass analysis of any individual, including human and non-human. It is unpredictable as to whether or not a polymorphisms ink the KChIP1 nucleic acid is SG05S808 exists in any non-human organisms, and whether or not detection of a polymorphism in such a sequence in any other organism would be predictive of the risk of type II diabetes mellitus. Mummidi et al. teaches the sequence analysis of the CC chemokine receptor 5 (CCR5) gene in humans and non-primates (Mummidi et al. The Journal of Biological Chemistry, Vol. 275, No. 25, pages 18946-18961). Notably, the reference teaches that the substantial interspecies sequence variation is observed for the cis-regulatory regions of the CCR5 gene (p. 18949, right column, 1st full paragraph). Thus it is entirely unpredictable as to whether or not any polymorphism, including marker SG05S808 would be associated with type II diabetes in any other non-human organism.

Some of the rejected claims encompass analysis of any polymorphism or haplotype that encompasses any polymorphism of a SLIT-3 nucleic acid. A polymorphism in a SLIT-3 nucleic

acid can be an insertion or deletion of a single nucleotide, more than one nucleotide, change of at least one nucleotide, deletion of several nucleotides, insertion of several nucleotides, duplication of all or part of the gene. Here, the genus of potential polymorphisms or haplotypes within the scope of the claimed invention is enormous, as a SLIT-3 nucleic acid could be polymorphic in hundreds or thousands of different ways. The specification demonstrates that even once a polymorphism is identified, it is not predictable whether that particular polymorphism will be predictive of susceptibility to type II diabetes. The specification teaches the testing of 106 different polymorphic markers (29 microsatellites and 77 SNP) and found that only thirteen of these demonstrated a statistically significant relationship with type II diabetes. Further, six of these thirteen are microsatellite markers, and for these, incomplete disclosure as to the This exemplifies that not all polymorphisms within the SLIT-3 gene are associated with Type II diabetes. The specification gives ten haplotypes that are more frequently present in individuals with Type II diabetes, but there is no apparent common structural feature among these haplotypes. And, these haplotypes are comprised of microsatellite alleles for which there is no adequate written description.

Some of the rejected claims encompass detection only of the DG5S881 as a marker for susceptibility. There is no evidence in the specification that alleles of this polymorphism are associated with susceptibility to type II diabetes. In fact, there is evidence to the contrary, as when this polymorphism was tested in single marker analysis, it was not reported as being significantly associated with type II diabetes (Table 4). Furthermore, even if it were, the specification does not provide any guidance as to what alleles of this marker are present in human populations, and in particular, which alleles are indicative of disease susceptibility. Table

2 provides a number of haplotypes that contain this marker which are associated with type II diabetes, but there is no guidance as to how the allele of DG5S881 present in these haplotypes is like or different from the molecule disclosed in figure 12D. The recitation of presence of polymorphism DG5S881 does not limit the polymorphism to a specific position in a specific nucleic acid sequence and could encompass the same or different positions in different species for example human, dog, hamster, etc.

The technology area of determining the association between alleles of polymorphisms and disease is highly unpredictable, and this is particularly so for type II diabetes. Barroso et al. (Diabetic Medicine 2005, 22:517-535) teach that evidence of genetic component of type II diabetes is a result of underlying differences in genes, with different frequencies of predisposing alleles present in different populations (see page 517, 2nd column, 1st paragraph). Barroso et al. teach that diabetes is not one but many diseases with a common phenotype and this makes the genetic studies harder to undertake as the definition of the disease can vary between studies. Barroso et al. teach that the problem is that it has been difficult to clinically distinguish each of the different categories of diabetes (see page 518, 2nd column, last paragraph). Barroso et al. teach that the understanding of the molecular bases of complex disease is still in its infancy and the identities of genes predisposing to many complex disorders, not just type II diabetes, remain elusive. Barroso et al. teach that several features of complex diseases are at the root of this – variable age of onset, reduced penetrance (the presence of different degrees of disease severity), locus and allelic heterogeneity as well as the presence of phenocopies means that many genes in multiple biological pathways are likely to interact with environment to increase or decrease susceptibility, many genes are expected to have a role in complex diseases each with a small

effect (see pg. 523, 2nd column, 2nd and 3rd full paragraph). Barroso et al. further teaches that few associations have been replication in additional populations (see page 525, 1st column, 1st paragraph). Therefore, Barroso et al. teaches that unpredictability of associating allele frequencies and polymorphism detection in type II diabetes in any ethnic group. Therefore, Barrosos et al. teaches the unpredictability of associating allele frequencies and polymorphism detection in type II diabetes risk.

Additionally, Ionnidis (Plost Med, 2005, 2(8):e124) teach that most published research findings are false. Ionnidis et al. teach that ill-founded strategy of claiming conclusive research finding solely on the basis of a single study assed by formal statistical significance represented and summarized by p values (see pg. 0696, 2nd column, 1st full para.) Ionnidis et al. teach that research findings are likely to be true that in fields that undertake large studies, such as randomized controlled trials (several thousand subjects randomized) than in small studies such as sample sizes 100 fold or smaller (see pg. 0697, 3rd column, 2nd full para.) Ionnidis et al. teaches that what matters is the totality of evidence and that statistical significance of a single study only gives a partial picture (see pg. 0701, 1st column). Hattersley et al. (Lancet, 2005, vol 366, pp. 1315-1323) teaches that the key quality in an association study is sample size (see page 1318, 2nd column, 1st full paragraph). Hattersley et al. teach that sample sizes of thousands are needed to detect variants that are common but have low relative risk and teach that allelic odds ratio of 1.1 to 2.0 requires the number of controls to be in thousands (see page 1318, 2nd column, 1st full paragraph and table 3). Hattersley et al. further teaches that emphasis has been on the need for greater stringency in the association studies in order to prove a given association and suggest a p value of $5x10^{-8}$, however arguments from Bayesian perspective suggest that $5x10^{-5}$ should be

sufficient to constrain the false discovery rate. It is further relevant to point out that Hegele teaches the general unpredictability in associating any genotype with a phenotype (Hegele 2002, Arterioscler. Thromb. Vasc. Biol. 22:2058-1061). Hegele teaches that often initial reports of an association are followed by reports of non-replication and refutation (p.1058, right col., lns.24-30). Hegele provides a table indicating some desirable attributes for genetic association studies (p.1060), and includes choosing an appropriate significance threshold (see 'Minimized type 1 error (FP)') and replication of results in independent samples (see 'Replication'). Additionally, Hegele teaches the desirability of a likely functional consequence predicted by a known or putative functional domain.

Given the lack of guidance in the specification with regard to association of polymorphisms within SLIT-3 nucleic acid and increase OR decrease likelihood of diagnosis of type II diabetes mellitus along with the evidence in the art that demonstrates the unpredictability of associating genotypes with type II diabetes, the quantity of experimentation in this area is extremely large. The skilled artisan would have to perform an extremely large study and include different populations and familial studies each polymorphism and each haplotype of SLIT-3 to determine if in fact there was either an association between the polymorphism any individuals and type II diabetes mellitus. The results of such a study are clearly unpredictable as evidence by the post filing art (which reflects the current state of the art) and the teachings in the specification which failed to demonstrate a single marker association between the DG5S881 marker and type II diabetes.

In order to practice the invention as broadly as it is claimed, the skilled artisan would have to determine polymorphisms in SLIT-3 that are indicative of susceptibility to type II

diabetes, and when present determine which alleles are so indicative. There are a limited number of possibly associated SNP given in Table 4, and for these specific embodiments, enablement may be present. These are non-elected embodiments. There is no apparent common structural feature among the polymorphisms that were identified as being associated, and so, these are not sufficient to support enablement for the entire breadth of the generic claims.

The skilled artisan would have to perform an extremely large amount of trial and error analysis in a large study to determine if such polymorphisms would predictably determine a susceptibility to type II diabetes mellitus. Given the lack of guidance in the specification and the post filing art with respect to accurately testing genetic diseases, such analysis is replete with unpredictable experimentation and is considered undue.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Tuesday or Wednesday, from 9:00 AM until 4:30 PM, and Thursday afternoon from 12:30 PM until 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached by calling (571) 272-0763.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Juliet C. Switzer/
Primary Examiner
Art Unit 1634

May 7, 2009